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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/685,296	10/10/2000	Douglas D. Randall	UMO-1482.1	4557

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SENNIGER POWERS LEAVITT AND ROEDEL
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EXAMINER
KALLIS, RUSSELL

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 08/29/2002

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/685,296	Applicant(s) RANDALL ET AL.	
	Examiner Stuart Baum	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,8,12,16,20-24 and 28-44* is/are pending in the application.

4a) Of the above claim(s) *4,8,12,16,20-24 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *02/01/01* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group III in Paper No. 7 is acknowledged. The traversal is on the ground(s) that a search of the Groups as defined by the Office will involve substantially overlapping searches and that this would not constitute a serious burden. This is not found persuasive because an assertion of "substantially overlapping" is not sufficient grounds to rescind the requirement for restriction of the claims of the instant application into patentably distinct groups filed 4/22/2002. The aforementioned Groups I and II differ in composition, structure, and function; while Groups III-VIII are capable of, and require, separate manufacture as claimed because they differ in the combination of DNAs that they encompass and will have a different genotype and phenotype; and hence, different searches and considerations would be required for examination of the different plants. The following is a selection from MPEP § 803:

DISTINCT

> The term "distinct" means that two or more subjects as disclosed are related, for example, as combination and part (subcombination) thereof, process and apparatus for its practice, process and product made, etc., but are capable of separate manufacture, use, or sale as claimed, AND ARE PATENTABLE (novel and unobvious) OVER EACH OTHER (though they may each be unpatentable because of the prior art). It will be noted that in this definition the term related is used as an alternative for dependent in referring to subjects other than independent subjects.
> It is further noted that the terms "independent" and "distinct" are used in decisions with varying meanings. All decisions should be read carefully to determine the meaning intended.

Under the statute an application may properly be required to be restricted to one of two or more claimed inventions only if they are able to support separate pat-ents and they are either independent (MPEP § 806.04 - § 806.04(i)) or distinct (MPEP § 806.05 - § 806.05(i)).

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims an enzyme having E1α, E1β, and E2 subunits from any source and any sequence, and any enzyme of any source and sequence that enhances the biosynthesis of 2-oxobutyrate.

Applicant describes cDNA clones from *Arabidopsis* of E1α and E1β subunits of pyruvate dehydrogenase complex having 5' regions upstream of the coding region for the mature polypeptide similar to a chloroplastic transit peptide (Example 1 page 52 lines 25-31, and page 53 lines 13-16), a cDNA clone from *Arabidopsis* of an E2 subunit of pyruvate dehydrogenase complex with a 5' region upstream of the coding region for the mature polypeptide similar to a chloroplastic transit peptide (Example 2 page 64 lines 3-17), a cDNA clone from *Arabidopsis* of

an E1α subunit of a branched chain oxoacid dehydrogenase complex with an incomplete 5' region upstream of the coding region for the mature polypeptide similar to a mitochondrial transit peptide (Example 3 pages 65-66), a cDNA clone from *Arabidopsis* of an E1β subunit of a branched chain oxoacid dehydrogenase complex with no indication of any organellar target sequence (Example 4 pages 67-68), and a cDNA clone from *Arabidopsis* of a dihydrolipoamide S-acyltransferase E2 subunit of the branched chain oxoacid dehydrogenase complex with no indication of any organellar target sequence (Example 5 pages 69-70), and engineered chimeric E1α and E1β subunits of the branched chain oxoacid dehydrogenase of *Arabidopsis* (Example 6 pages 70-76).

Applicant does not describe all E1α, E1β, and E2 subunits of the branched chain oxoacid dehydrogenase complexes from all organisms other than *Arabidopsis,* or any other protein from any source that somehow "enhances the biosynthesis of 2-oxobutyrate".

See *University of California V. Eli Lilly and Co.,* 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining a cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

The court also addressed the manner by which genus of cDNAs might be described: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.* At 1406.

Given the claim breadth and lack of guidance as discussed above, the specification does not provide an adequate written description of the claimed invention.

4. Claims 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant broadly claims a plant comprising the E1α, E1β, and E2 subunits of any pyruvate dehydrogenase complex from any source and of any sequence, and a plant comprising any pyruvate dehydrogenase complex with any one of the E1α, E1β, or E2 subunits from the mitochondrial form of pyruvate dehydrogenase complex. Applicant also broadly claims a plant comprising any protein that somehow "enhances the biosynthesis of 2-oxobutyrate".

Applicant teaches cDNA clones from *Arabidopsis* of E1α and E1β subunits of pyruvate dehydrogenase complex having 5' regions upstream of the coding region for the mature polypeptide similar to a chloroplastic transit peptide (Example 1 page 52 lines 25-31, and page 53 lines 13-16), a cDNA clone from *Arabidopsis* of an E2 subunit of pyruvate dehydrogenase complex with a 5' region upstream of the coding region for the mature polypeptide similar to a chloroplastic transit peptide (Example 2 page 64 lines 3-17), a cDNA clone from *Arabidopsis* of an E1α subunit of a branched chain oxoacid dehydrogenase complex with an incomplete 5' region upstream of the coding region for the mature polypeptide similar to a mitochondrial transit peptide (Example 3 pages 65-66), a cDNA clone from *Arabidopsis* of an E1β subunit of a branched chain oxoacid dehydrogenase complex with no indication of any organellar target sequence (Example 4 pages 67-68), and a cDNA clone from *Arabidopsis* of a dihydrolipoamide

S-acyltransferase E2 subunit of the branched chain oxoacid dehydrogenase complex with no indication of any organellar target sequence (Example 5 pages 69-70), engineered chimeric E1α and E1β subunits of the branched chain oxoacid dehydrogenase of *Arabidopsis* (Example 6 pages 70-76), and targeting of the branched chain oxoacid dehydrogenase complex E1α, E1β, and E2 subunits to the plastid to enhance propionyl-CoA poduction from 2-oxobutyrate (Example 7 page 76, lines 26-29).

Applicant does not teach plants transformed with any one of the many branched chain oxoacid dehydrogenase complexes from plants or microbes, any non-exemplified protein that somehow "enhances 2-oxobutyrate biosynthesis", or plant transformation with any combination of the various subunits of said complexes, and any enhancement of 2-oxobutyrate biosynthesis therefrom.

The state of the art for mixing subunits across species of multimeric enzymatic complexes is highly unpredictable. The specific effects with respect to functionality and specific activity cannot be anticipated with any degree of predictability and one of skill in the art must rely upon empirical determination. The subunits of a multi enzyme complex or any protein protein interaction associate through conserved amino acid side groups, and the absence of any number of those associations will most likely occur when mixing subunits from various species, and hence deter or eliminate the formation of a functional complex. The ability to form cross species heterodimers of ornithine decarboxylase was studied in a comparison between two parasitic protozoa, *L. donovani* and *T. brucei*, with respect to the mouse ornithine decarboxylase. The inability of ornithine decarboxylase from *L. donovani* to form heterodimers with ornithine decarboxylase from either *T. brucei* or mouse is thought to have its origins in the 40% sequence

identity that *L. donovani* has with both *T. brucei* and mouse ornithine decarboxylase. The homodimer of *L. donovani* ornithine decarboxylase is thermodynamically more favored, because of the conserved specific amino acid side group interactions, over formation of the hetrodimer of *L. donovani* ornithine decarboxylase and *T. brucei* or mouse ornithine decarboxylase upon renaturation (Osterman *et al.* Biochemistry, Vol. 33, 13662-13667, pp. 13666 column 2, lines 39-48). Thus, the ability to recover activity by an indiscriminate mixing of subunits of enzymes from across a broad range of species having the same substrate preference is unpredictable due to changing amino acid residues that have been selected for maximizing specific interactions between subunits over evolutionary time. This is illustrated in the example of a site directed mutant of *Chlamydomonas reinhardtii* Rubisco P89R and wild type Rubisco activase from spinach and Tobacco whereby a single amino acid substitution in the *Chlamydomonas* Rubisco large subunit resulted in a significant change in activation preference from spinach Rubisco activase to Tobacco Rubisco activase and a significant loss in activity (Larson *et al.* J. of Biol. Chem., Vol. 272, No. 27, July 4 1997, pp. 17033-17037, Abstract, page 17035, Figure 4, and page 17036 column 1, lines 8-12).

Given the lack of guidance, the lack of working examples in the specification, the breadth of the claims, and the unpredictability in the art, undue trail and error experimentation would have been required by one skilled in the art to identify and isolate genes encoding a multitude of subunit combinations from across the evolutionary spectrum, or to identify and isolate genes encoding a multitude of proteins which somehow "enhance 2-oxobutyrate synthesis", and to evaluate the ability of these genes when introduced into a multitude of plants for those unique combinations that would result in an enhancement of the biosynthesis of 2-oxobutyrate.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 29-30 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

At Claim 29, line 1, "a plant" is indefinite. It is unclear whether "a plant" refers to transformed or untransformed plants or of any particular species.

At Claim 29, line 3, "enhances" is indefinite. It is unclear whether "enhances" is meant to be an increase in the amount of product, or more or less regulation of production of the product, or to include some novel biochemical improvement to the product itself.

7. Claims 29-30 are deemed free of the prior art, given the failure of the prior art to teach or reasonably suggest plants containing all of the recited enzymes, either naturally or by transformation.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (703) 305-5417. The examiner can normally be reached on Monday-Friday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding, or if the examiner cannot be reached as indicated above, should be directed to the legal analyst, Sonya Williams, whose telephone number is (703) 308-0009.

Russell Kallis Ph.D.
August 13, 2002

DAVID T. FOX
PRIMARY EXAMINER
GROUP ~~180~~ 1638